Chapter 1
History and Current Status of Online Haemodiafiltration

Bernard Canaud and Ingrid Ledebo

Abstract The genesis of hemodiafiltration (HDF) has followed the general sequence of any new therapy passing through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step.

In the conceptual phase unmet needs of end stage kidney disease patients treated by hemodialysis were identified, proof of concept was established and the necessary technological development took place.

During the development phase short-term clinical studies demonstrated the safety and efficacy of the online HDF and long-term clinical studies gave evidence of benefits and risks of this new renal replacement modality.

After having satisfied these different steps, any remaining questions and/or uncertainties can be formulated and the future of the therapy can be discussed. In these entire phases one can identify key discoveries and applications that have contributed to major steps forward, often in a new direction.

In this chapter, we have highlighted such events and discussed their importance.

Keywords End stage chronic kidney disease • Renal replacement therapy • Online substitution fluid • Cold sterilization process • Convective dose

Introduction: Why Hemodiafiltration Was Needed?

The development of a new renal replacement therapy corresponds to a need expressed by the nephrology community to correct for shortfalls and/or side effects observed with the use of conventional dialysis. Looking back at the 1970s,

B. Canaud, PhD (✉)
Emeritus Professor of Nephrology, Center of Excellence Medical, Fresenius Medical Care Deutschland GmbH, Else-Kröner-Straße 1, Bad Homburg v.d.H. 61352, Germany

University of Montpellier, School of Medicine, Montpellier, France
e-mail: Bernard.Canaud@fmc-ag.com

I. Ledebo, PhD
Director Scientific Support Gambro 1980–2012, Lund, Sweden

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_1

conventional hemodialysis was performed with low-flux cuprophane membranes, acetate as buffer source and simple pressure devices to control ultrafiltration. The majority of patients were treated in 4–5 h sessions two to three times per week. As a result, efficiency was limited to small water soluble uremic toxins, cardiovascular tolerance was poor and problems with bioincompatibility and dialysis-related pathology started to appear (amyloidosis, accelerated ageing and – atherosclerosis). These factors were pointed out as limitations for long-term sustainability of this supportive therapy. A need for improving hemodialysis treatment both on the short term by improving efficacy and tolerability and on the long term by reducing side-effects was the main focus of clinical research at the time.

The development of a new therapy follows the general sequence of any new therapeutic agent and goes through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step. In the conceptual phase unmet needs are identified, proof of concept is established and the necessary technological development takes place. During the development phase short-term clinical studies demonstrate the safety and efficacy of the therapy and long-term clinical studies give evidence of benefits and risks. Major milestones achieved in online HDF development over the last four decades has been summarized in Fig. 1.1.

When this is satisfactorily shown any remaining questions and uncertainties are formulated and the future of the therapy can be discussed. In all these phases one can identify key discoveries and applications that have contributed to major steps forward, often in a new direction. For the therapy in focus in this handbook, hemodiafiltration (HDF), we would like to highlight such events and discuss their importance.

Conceptual Phase: How Did We Get There?

Unmet Needs

Renal replacement therapy (RRT) was successfully developed during the 1970s but end stage kidney disease (ESKD) patients were still faced with a high morbidity and mortality risk dominated by cardiovascular diseases [1, 2]. Although the exact

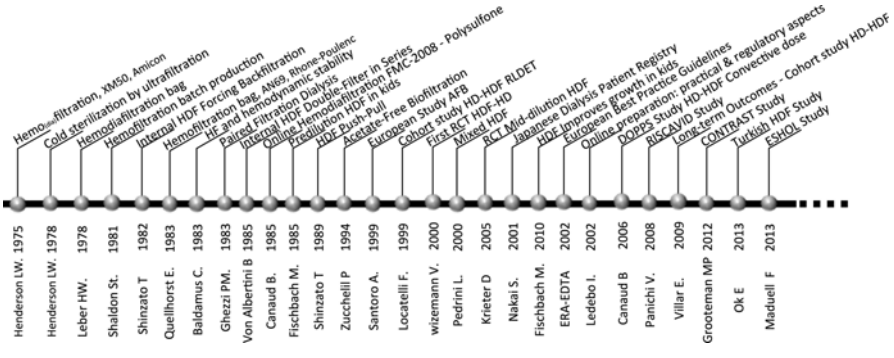

Fig. 1.1 Major milestones achieved in online HDF development over the last four decades

reasons for these shortfalls were not clear, one can acknowledge that they were multifactorial including patient and comorbid risk profile, past history of chronic kidney disease (CKD) and care management before starting dialysis, and RRT efficacy and tolerance.

Considering the pioneering work of Babb [3] and Bergstrom [4, 5], later updated and completed by the Eutox group [6] and others, it becomes clear that uremic toxins comprise a large spectrum of compounds characterized by molecular weights, chemical characteristics, kinetics, protein and tissue binding capacities that extends far beyond that of urea. Focusing on the 'middle and larger molecule' substances it is also obvious that these compounds can only be cleared by means of large pore size membranes and the addition of a driving force such as convection to solute fluxes.

Proof of Concept

In 1975 Henderson et al. using a synthetic ultrafiltration membrane (XM50, Amicon, USA), reported the first clinical application of hemofiltration (HF), although at the time referred to as "hemodiafiltration" [7, 8], see Fig. 1.2. The driving force for this new therapy was the desire to remove "middle molecules", i.e. uremic solutes that were putatively held responsible for some pathophysiologic manifestations of uremia and which could not be cleared in conventional low-flux HD because of their size. Henderson could show that by using pure convective therapy (HF) it was possible to extend the blood purification to include a wide range of large solutes, normally removed by the kidneys. The clinical study also showed that the patients tolerated the HF sessions much better than their regular HD. Fluid removal to reach dry weight was better achieved without symptoms [9, 10]. Correction of hypertension and a high degree of clinical wellbeing was noted among the patients although acetate was used as main buffer [11]. These results led to great expectations from the nephrology community. HF was perceived as a superior dialysis therapy and several groups started clinical trials.

In Europe, Quellhorst pioneered a large HF program using a new high-flux membrane (AN69, Rhone-Poulenc) and conducted controlled crossover studies on patients treated with HD and HF [12, 13]. He and others could show significant improvement of vascular stability and reduced incidence of symptomatic hypotension when patients were treated with HF [14, 15]. These results were presented in the late 1970s, at a time when the hopes of identifying the "middle molecules" were dwindling [16, 17]. HF was still considered an attractive therapy, more because of the improved hemodynamic stability than because of the capacity to remove large solutes. In 1981, Shaldon predicted: "In at least 20–30 % of patients, progress from classical diffusion dialysis will benefit the patient and at the same time improve cost-effectiveness by shortening treatment time, reducing staff requirement and offer better rehabilitation prospects" [18].

During the 1980s, based on urea kinetic modeling (UKM), Gotch and Sargent [19, 20] introduced the concept of dialysis quantification and established Kt/V as the dialysis dose index. Urea was used in this approach as an indicator of dialysis

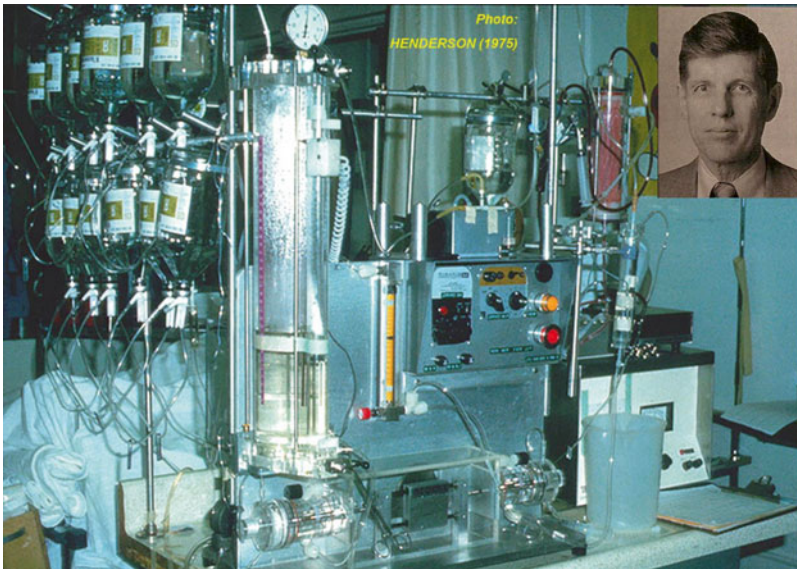

Fig. 1.2 LW Henderson and the first hemo(dia)filtration machine (Reprinted from Henderson et al. [7]. With permission from Elsevier)

efficacy, protein catabolic rate and dietary protein intake, and a surrogate of uremic toxins derived from protein metabolism [21]. Dialysis dose (Kt/V) became a new driving force and focus in the dialysis world for dialysis research and prescription [22]. With the prospect of reducing treatment times and optimizing performances all means were used to enhance the removal of urea. The determinants of diffusive transport – blood flow rate, dialysis fluid flow rate, surface area and permeability properties of the dialysis membrane (KoA) – were all adjusted upwards [23–25]. This meant that HF, which only applies convection and thus provides the same clearance for urea as for larger solutes, was no longer interesting with the ultrafiltration volumes used at the time (20–25 L/session) [26, 27]. However, there were still some pioneering groups in research-oriented hospitals who had experienced the clinical benefits of HF therapy and explored larger ultrafiltration volume to match performances with new standards [28].

During the late 1970s and early 1980s the dialysis industry thrived thanks to the growing number of ESKD patients. Ambitious development projects were started in collaboration with academia and resulted in new membranes and technical innovations that were applied in experimental therapies. One such innovative therapy was the combination of HD and HF, sometimes referred to as "simultaneous HF/HD" and later renamed hemodiafiltration. The entrepreneur group in Giessen, having worked with both HD and HF, felt that each therapy had something to offer [29]. Their goal was to achieve enhanced clearance for small as well as large solutes while maintaining good hemodynamic stability. By combining regular high-flux hemodialysis and forced ultrafiltration with substitution fluid provided in sterilized bags, this group opened a new therapeutic avenue named hemodiafiltration [30, 31].

Technological Development

HDF is technically complex to perform because it requires components needed for both HD and HF [32]. The membrane in the filter should have good diffusive properties, high hydraulic permeability for easy ultrafiltration and generous sieving profile to allow passage of solutes up to the size of albumin. Because the fluid is used for both diffusion and convection, it must meet the corresponding quality requirement, i.e. the dialysis fluid should be at least ultrapure and the substitution fluid be sterile and non-pyrogenic. The fluid composition should be individualized within physiological limits. Access to fluid must not be a limiting factor, which makes on-line preparation integrated with the treatment the only option. This places special hygienic and regulatory demands on the hardware, in addition to accurate volume control and all other functions in modern dialysis equipment.

Technical limitations, mainly regarding membrane permeability and fluid composition and volume, have been the major determinants of the development of HDF therapy during the course of the 35 years it has been applied. The membranes used in the early days were suited for diffusive or convective transport respectively but have been gradually developed and optimized for HDF. Modern membranes combine high diffusive and hydraulic permeability with generous but controlled sieving of solutes. To achieve these characteristics membranes are today made from various synthetic polymers, which can be combined to provide optimal biocompatibility as well as the desired performance.

The fluids have also undergone major changes. In the first HDF trials and for many years the buffer source was acetate in the dialysis fluid, as in HD, and lactate in the substitution fluid provided in autoclaved bags, as in HF. When bicarbonate was introduced in the dialysis fluid, it still took many years until it was included in the substitution fluid. Based on cold sterilization, as described earlier by Henderson [33], Canaud et al. introduced and evaluated for the first time in clinic on-line HDF with bicarbonate using a using a modified HD machine with fluid balancing chambers to control ultrafiltration [34]. After this pilot trial, the feasibility of on-line fluid preparation was recognized and the advantages became apparent. On-line preparation of the sterile fluid used for substitution meant not only that bicarbonate could be used and the electrolyte composition could be individualized. It also made it possible to increase the dose of therapy by exchanging larger fluid volumes, which for practical and economical reasons had been restricted to small research studies when fluid in autoclaved bags were used. Different substitution modalities have been developed to overcome patient barriers and/or to achieve targeted efficacy of the method in peculiar conditions (pre-dilution, mid-dilution and mixed-dilution) [35–38]. It was not until on-line fluid preparation became widely accepted, which with some exceptions occurred in the new millennium, that the limitations imposed by fluid issues were resolved [39–41].

Although described above as a technical limitation the general introduction of on-line fluid preparation should probably be viewed as a regulatory limitation [42]. The ultrafilters required for stepwise removal of bacteria and pyrogens from dialysis fluid were commercially available already in the mid-1980s and prototype systems

for on-line preparation of large volumes of sterile, non-pyrogenic fluid were originally used for HF. However, sterilization by on-line preparation is still not recognized by the Pharmacopoeia and therefore not considered by regulatory authorities, so the approval of dialysis machines with on-line capacity met with serious resistance [43, 44].

In some countries, nephrologists managed to convince authorities to approve on-line HF and HDF, but only with cumbersome safety measures attached to the application, which increased labor and cost [45, 46]. Other countries lacked regulations and practicing nephrologists hesitated to use the therapy. Alternative and/or hybrid therapies have been developed to bypass those regulatory measures and/or to explore additional benefits such as acetate-free biofiltration (AFB) and paired filtration dialysis (PFD) or hemodiafiltration with endogenous reinfusion of substitution fluid after regeneration on resin (HFR) [47–50]. Still, the accumulated European experience on the safety of performing on-line HDF and the potential of the promising data from patients treated with on-line HDF finally broke the barrier and during the new millennium on-line HDF is the only form of the therapy considered [51]. An international guideline covering practical and safety aspects of on-line fluid preparation is now widely approved as standard [52].

While waiting for authorities to approve on-line fluid preparation some groups, mainly in Japan and the US where on-line equipment was not commercially available, developed their own systems for performing diffusion and convection at the same time, without using external fluid for substitution [53–56]. They designed systems that increased ultrafiltration by various pressure manipulations and relied on backfiltration of dialysis fluid to compensate for excess ultrafiltration. This can increase the convective transport compared to HD but not to the extent of optimally prescribed on-line HDF. In addition, the fluid quality may be a problem.

Representing the best of both extracorporeal therapies (HD and HF), hemodiafiltration (HDF) has attracted much interest throughout the western world, i.e. Europe, Japan and the USA, from the early 1980s and it still does, although the therapeutic application and the questions asked have undergone major changes [57]. Considering these changes in the development of the therapy, clinical results from different time periods reflect what could be achieved with the products available at that time, and comparison with modern therapy should be avoided [58].

Clinical Implementation: What Are the Results?

Safety

Online preparation of substitution solution by cold sterilization process from fresh dialysis fluid is a fundamental prerequisite for delivering high-volume HDF and HF modalities. The potential of bacterial-derived products (endotoxin, peptidoglycans, bacterial DNA) entering the bloodstream in case of cold sterilization failure or inadequate disinfection of HDF machine is an important consideration. By applying

strict hygienic rules of disinfection to the online HDF machine, stringent microbial monitoring and periodical replacement of sterilizing ultrafilters, any risk may be virtually abolished. Online blood purification modalities necessitate the use of ultrapure water and certified machines, and the compliance to strict hygienic rules that have been detailed elsewhere [59]. For further reading, see Chap. 3. Several studies have confirmed the safety of the online HDF provided the adequate HDF machines are used and the best clinical practices are applied [60, 61]. The CONTRAST study confirmed in 10 centers over more than 20,000 HDF sessions the reliability and safety of the method [62]. As good clinical practice, it is advisable to monitor clinical symptomatology of HDF treated patients and to ensure measurement of blood sensitive CRP on a monthly basis [63].

HDF Versus HD in Short and Mid-term Studies

During the 1980s the dialysis industry was influenced by the interest in convective therapies and introduced a number of associated technological innovations. New membranes with increased hydraulic permeability, so called high-flux membranes, were made from synthetic polymers and showed improved biocompatibility when exposed to blood. Fluid removal during dialysis was simplified and made more accurate by the incorporation of ultrafiltration control systems in the dialysis equipment. New mixing devices facilitated the inclusion of bicarbonate in the dialysis fluid and acetate was gradually replaced as buffer source.

Although the development of these innovations was triggered mainly by the widespread interest in HF and HDF, they could all be used for HD. Performing HD with high-flux membranes, ultrafiltration control and bicarbonate changed the therapy significantly. The high-flux membrane allowed for increased ultrafiltration, which did not cause excess fluid removal because of the volume was controlled. By means of ultrafiltration controller devices in the HD machine, the excess ultrafiltration was compensated by backfiltration of dialysis fluid. This provided convective clearance, because the membrane was open and because the ultrafiltration was increased [64, 65]. The presence of bicarbonate, and even more so the absence of acetate, enhanced the hemodynamic stability and improved dialysis symptomatology [66, 67]. When high-flux HD was compared with the form of HDF used at the time, so called classical HDF with 9–10 L substitution fluid in bags, which provided around 10–12 L of convective volume, the difference in clearance and symptomatology could not always be detected [68, 69].

When the 1980s changed into the 1990s, urea kinetic monitoring still controlled the prescription of dialysis. Classical HDF provided similar or only slightly higher urea clearance than high-flux dialysis, but was considered more cumbersome to perform and was definitely more expensive, so unless favored by reimbursement it was of little interest to the urea-believers [70, 71]. However, at this time a large retention molecule, β_2-microglobulin (β_2m), appeared on the scene, calling for convective removal [72–74]. Problems with β_2m retention were taken

seriously, especially in Europe and Japan, where more effective and more biocompatible convective therapies were again discussed [75–78]. Both HF and HDF were tested in clinical studies using on-line equipment and large convection volumes [79–84]. Towards the end of the 1990s the flaws of urea kinetic modeling and its consequence, reduced treatment times and poor outcome, became apparent to the dialysis community and studies were designed to test new therapeutic alternatives [85, 86].

In 2002 the HEMO study could not show any difference in survival between patients treated with either low or high urea dose or low-flux or high-flux membranes. A subgroup analysis showed improved survival in long-term dialysis patients treated with high-flux filters and the HEMO investigators made the reservation that "the higher β_2m clearances achievable with HDF might improve outcomes" [87].

HDF in Long-Term Studies: Patient Outcome

The ultimate benefits of HDF/HF therapies in terms of "hard clinical endpoint" such as reduction of β2-M-amyloidosis risk, improved survival and reduced hospitalization that were suggested by retrospective studies have been confirmed by recent prospective randomized controlled trials [88–91]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) first suggested that patients being treated with high-efficiency HDF (15–25 L/session) had a 35 % lower mortality than those treated with low-flux hemodialysis; comparison with high-flux hemodialysis and low-efficiency HDF (<15 L/session), however, was not significantly different [92]. Two recent prospective randomized trials (CONTRAST and Turkish HDF study) failed to show beneficial effects on mortality (all-cause or CV mortality) as primary endpoint. Interestingly, both studies showed, in post-hoc analysis, beneficial effects on all-cause mortality when patients were stratified and allocated to high ultrafiltration volume (>20 L/session), i.e. to high convective dose [93, 94]. The importance of best clinical practices and weakness of these studies was identified since 50–66 % of patients enrolled did not achieve the targeted ultrafiltration volume [95]. The most recent randomized controlled trial, the Catalonian ESHOL study, complying with best clinical practices and achieving targeted ultrafiltration volume in 90 % of patients proved that mortality was reduced by 30 % (all-cause and CV cause) in high-volume HDF treated patients. In addition, the Catalonian study found a reduction of hypotensive episodes (28 %), stroke (61 %) and infection (55 %) [96]. For further reading, see Chap. 16.

Convective Dose Concept

The burning question in HDF today concerns the effective convection volume, i.e. the total undiluted ultrafiltration volume [97–99]. How large should it be to make a difference and how can we best obtain it? To answer this question, a group of

Dutch nephrologists designed the CONTRAST study aiming for 24 L of ultrafiltration, i.e. convection volume, per treatment but only achieved an average of 20.7 L [95, 100]. *Post hoc* analysis showed that the tertiles of patients treated with the highest convection volume, >21.95 L, had significantly improved survival [83]. In parallel a similar study was conducted in Turkey, the Turkish study compared on-line HDF with high-flux HD, aimed for 15 L of infusion solution and achieved an average of 17.2 L [94]. The result was similar to CONTRAST in that no difference in survival could be shown for the total population, but again a *post hoc* analysis of HDF patients treated with the highest convection volume, >21 L (17.4 L substitution + 3.5 L weight loss), had significantly improved survival. The secondary result from these two large, randomized, controlled studies was confirmed by the ESHOL study, which in the primary analysis showed that all patients treated with HDF with convection volumes exceeding 22.9 L per session had significantly improved survival compared with patients on high-flux HD [86]. Further information on the pitfalls and reliability of RCTs and meta-analyses on this subject is provided in Chap. 16.

Remaining or Unsolved Questions Related to Online HDF: Where Are We Today?

Online hemodiafiltration is no longer an experimental treatment, it is a mature renal replacement therapy, used daily to sustain life of more than 160,000 ESKD patients worldwide including 80,000 in the EMEA region [101]. This is presented in Fig. 1.3. Online HDF represents the most advanced treatment modality for end stage kidney disease patients [102]. Considering results of recent RCTs, the time has now come for worldwide, including USA, acceptance of hemodiafiltration as the means to improve ESKD patient outcomes [103].

The use of highly permeable membranes submitted to high transmembrane pressure regime may lead to increased albumin loss, although improvement of membrane manufacturing technology has reduced the sieving coefficient of albumin and minimized losses [57]. For more porous or higher cut-off membranes that do leak albumin, HDF modality exposes the patient to risk significant albumin loss and may not be a good option. Nevertheless, clinical and biologic consequences of albumin loss and hypoalbuminemia must be balanced with the putative beneficial effect of increased removal of uremic toxin-bound substances.

Enhanced loss of nutrients is a theoretical risk associated with all modalities using high-flux membranes and enhanced convective fluxes. Soluble vitamins, trace elements, amino acids, small peptides, and proteins may be lost during high-flux treatments. The total amount of nutrients lost per session is, however, sufficiently low to be easily compensated for by adequate oral intake [104].

Electrolyte balance depends strongly on patient anthropometric characteristics, electrolyte concentrations and convective volume achieved during HDF sessions. Electrolyte prescription (Na, K, HCO3, Ca, Mg) needs to be customized to patient

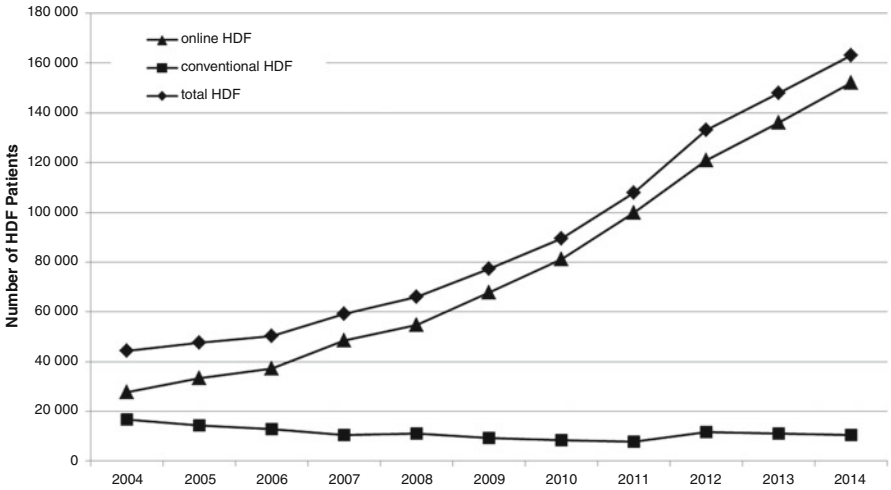

Fig. 1.3 Development of HDF patients from 2004 to 2014 (Based on data from Ref. [103])

metabolic needs and convective volume. Higher ultrafiltration volumes will need to reassess electrolyte mass balance and reset prescription accordingly, since all present reported studies have been performed with restricted ultrafiltration volume (<30 L/session in post-dilution HDF). For further reading, see Chap. 11.

Future Development of Online HDF

Modern online HDF equipment provides a unique technical platform that may be used to facilitate the implementation of new dialysis options (nocturnal HDF, daily HDF) or to revitilize home or self-care renal replacement therapies with automated functions such as auto-priming, rinsing or flushing. With liberal access to sterile apyrogenic fluid new applications can be developed without cost concern.

Conclusions

Online hemodiafiltration can today be considered a mature renal replacement therapy, being used daily to sustain life of more than 80,000 ESKD patients in Europe (18 % of all RRTs). By combining diffusive and convective clearances, online HDF offers the most efficient solute removal capacity over the widest molecular weight spectum of uremic toxins. With high-flux synthetic membrane and ultrapure dialysis fluid, online HDF constitutes the most hemocompatible renal replacement therapy. Safety and efficacy have been proven in numerous short and mid-term clinical studies. Recent randomized controlled clinical trials tend to accredit the superiority of online HDF over contemporary HD, i.e. high-flux HD, to the adequate convective

dose (or convective volume) being delivered. Further clinical trials should establish the optimal convective dose in different clinical settings (patient characteristics and/or ethnicity, substitution modalities) and to establish the cost-effectiveness of HDF compared to contemporary HD.

Teaching Points

- The genesis of hemodiafiltration (HDF) has followed the general sequence of any new therapy passing through a conceptual phase, a development phase and a long-term evaluation phase with adequate analysis in each step.
- In the conceptual phase:
  - Unmet needs of end stage kidney disease patients treated by hemodialysis were identified (high morbidity and mortality risk, retention of uremic toxins in the middle molecular weight range)
  - Proof of concept was established in 1975 (middle molecule removal by hemofiltration)
  - The necessary technological development took place (e.g. combination of hemodialysis with hemofiltration, improvement of dialyzer membranes, online preparation of substitution fluids).
- During the development phase:
  - Short-term clinical studies demonstrated the safety and efficacy of the online HDF.
  - The ultimate benefits of HDF/HF therapies in terms of 'hard clinical endpoint' (e.g. improved survival and reduced hospitalization) as suggested by retrospective studies have been confirmed by randomized controlled trials
- Finally, remaining questions and/or uncertainties can be formulated (e.g. the most effective convection volume, the consequences of loss of albumin and micro-nutrients, electrolyte balance).

References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med. 1974;290(13):697–701.
2. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9(12 Suppl):S16–23.
3. Babb AL, Ahmad S, Bergström J, Scribner BH. The middle molecule hypothesis in perspective. Am J Kidney Dis. 1981;1(1):46–50.
4. Bergström J, Fürst P. Uremic toxins. Kidney Int Suppl. 1978;8:S9–12.
5. Asaba H, Fürst P, Oulés R, Yahiel V, Zimmerman L, Bergström J. The effect of hemodialysis on endogenous middle molecules in uremic patients. Clin Nephrol. 1979;11(5):257–66.

6. Vanholder R, Baurmeister U, Brunet P, Cohen G, Glorieux G, Jankowski J, European Uremic Toxin Work Group. A bench to bedside view of uremic toxins. J Am Soc Nephrol. 2008;19(5): 863–70.
7. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med. 1975;85(3):372–91.
8. Henderson LW, Silverstein ME, Ford CA, Lysaght MJ. Clinical response to maintenance hemodiafiltration. Kidney Int Suppl. 1975;2:58–63.
9. Baldamus CA, Ernst W, Lysaght MJ, Shaldon S, Koch KM. Hemodynamics in hemofiltration. Int J Artif Organs. 1983;6(1):27–31.
10. Baldamus CA, Shaldon S, Koch KM. Cardiovascular stability in hemodialysis and hemofiltration. In: Cambi V, editor. 'Short Dialysis'. Topics in renal medicine, vol. 3. Boston: Martinus Nijhoff Publishing; 1987. p. 321–64. Chap 14.
11. Schünemann B, Girndt J, Quellhorst E. Hemofiltration as a treatment for "dialysis-resistant" hypertension and hypotensive hyperhydration. J Dial. 1977;1(6):575–83.
12. Quellhorst EA, Schuenemann B, Hildebrand U. Morbidity and mortality in long-term hemofiltration. ASAIO J. 1983;6(4):185–91.
13. Quellhorst EA, Schuenemann B, Mietzsch G. Long-term hemofiltration in "poor risk" patients. ASAIO Trans. 1987;33(3):758–64.
14. Baldamus CA, Quellhorst E. Outcome of long-term hemofiltration. Kidney Int Suppl. 1985;17:S41–6.
15. Quellhorst E, Hildebrand U, Solf A. Long-term morbidity: hemofiltration vs. hemodialysis. Contrib Nephrol. 1995;113:110–9.
16. Fürst P, Zimmerman L, Bergström J. Determination of endogenous middle molecules in normal and uremic body fluids. Clin Nephrol. 1976;3(2):178–88.
17. Nolph KD. Short dialysis, middle molecules, and uremia. Ann Intern Med. 1977;86(1): 93–7.
18. Shaldon S. Progress from hemodialysis. Nephron. 1981;27:2–6.
19. Gotch FA, Sargent JA, Keen M, Lee M. Individualized quantified dialysis therapy of uremia. Proc Clin Dial Transplant Forum. 1974;4:27–35.
20. Gotch FA, Sargent JA, Keen M, Lam M, Prowitt M, Grady M. Clinical results of intermittent dialysis therapy (IDT) guided by ongoing kinetic analysis of urea metabolism. Trans Am Soc Artif Intern Organs. 1976;22:175–88.
21. Gotch FA. Urea guided dialysis therapy. Current clinical results. Dial Transplant. 1976;5:15–8.
22. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526–34.
23. Shaldon S, Florence P, Fontanier P, Polito C, Mion C. Comparison of two strategies for short dialysis using 1m2 and 2m2 surface area dialysers. Proc Eur Dial Transplant Assoc. 1976;12:596–605.
24. Cambi V, Hampl H, Savazzi G, Arisi L, Bignardi L, Garini G, Rossi E, Paeprer P, Kessel M, Migone L. Trans Am Soc Artif Intern Organs. 1978;24:443–7.
25. Trafford JAP, Sharpstone P, Evans R, Ireland R. Evaluation of ultra-short dialysis. Br Med J. 1979;1:518–9.
26. Shaldon S, Beau MC, Deschodt G, Mion C. Mixed hemofiltration (MHF): 18 months experience with ultrashort treatment time. Trans Am Soc Artif Intern Organs. 1981;27:610–2.
27. Quellhorst E, Scheunemann B, Hildebrand U. Hemofiltration: an improved method of treatment for chronic renal failure. Contrib Nephrol. 1985;44:194–211.
28. Canaud B, Araujo A, Sany C, Farrell PC, Garred LJ, Shaldon S, Mion C. A urea kinetic model for haemofiltration. Life Support Syst. 1985;3(1):15–25.
29. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schütterle G. Hemodiafiltration: a new alternative to hemofiltration and conventional hemodialysis. Artif Organs. 1978;2(2):150–3.
30. Wizemann V, Kramer W, Knopp G, Rawer P, Mueller K, Schütterle G. Ultrashort hemodiafiltration: efficiency and hemodynamic tolerance. Clin Nephrol. 1983;19(1):24–30.
31. Wizemann V. Hemodiafiltration: an avenue to shorter dialysis? Contrib Nephrol. 1985;44:49–56.

32. Ledebo I, Blankestijn PJ. Haemodiafiltration-optimal efficiency and safety. NDT Plus. 2010;3(1):8–16.
33. Henderson LW, Beans E. Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int. 1978;14(5):522–5.
34. Canaud B, N'Guyen QV, Lagarde C, Stec F, Polaschegg HD, Mion C. Clinical evaluation of a multipurpose dialysis system adequate for hemodialysis or for postdilution hemofiltration/hemodiafiltration with on-line preparation of substitution fluid from dialysate. Contrib Nephrol. 1985;46:184–6.
35. Fischbach M, Attal Y, Geisert J. Hemodiafiltration versus hemodialysis in children. Int J Pediatr Nephrol. 1984;5(3):151–4.
36. Krieter DH, Falkenhain S, Chalabi L, Collins G, Lemke HD, Canaud B. Clinical cross-over comparison of mid-dilution hemodiafiltration using a novel dialyzer concept and post-dilution hemodiafiltration. Kidney Int. 2005;67(1):349–56.
37. Santoro A, Conz PA, De Cristofaro V, Acquistapace I, Gaggi R, Ferramosca E, Renaux JL, Rizzioli E, Wratten ML. Mid-dilution: the perfect balance between convection and diffusion. Contrib Nephrol. 2005;149:107–14.
38. Pedrini LA, De Cristofaro V, Pagliari B, Samà F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58(5):2155–65.
39. Ledebo I. On-line hemodiafiltration: technique and therapy. Adv Ren Replace Ther. 1999;6(2):195–208.
40. Spalding E, Farrington K. Haemodiafiltration: current status. Nephron Clin Pract. 2003;93(3):c87–96.
41. Canaud B. Online hemodiafiltration. Technical options and best clinical practices. Contrib Nephrol. 2007;158:110–22.
42. Ledebo I. On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol. 2002;13 Suppl 1:S78–83.
43. Pirovano D. Regulatory issues for on-line haemodiafiltration. Nephrol Dial Transplant. 1998;13 Suppl 5:21–3.
44. Pirovano D. Regulatory challenges of on-line hemodiafiltration. Contrib Nephrol. 2011;175:69–73.
45. Martin K, Laydet E, Canaud B. Design and technical adjustment of a water treatment system: 15 years of experience. Adv Ren Replace Ther. 2003;10(2):122–32.
46. Canaud B, Bosc JY, Leray H, Morena M, Stec F. Microbiologic purity of dialysate: rationale and technical aspects. Blood Purif. 2000;18(3):200–13.
47. Zucchelli P, Santoro A, Spongano M. Acetate-free biofiltration: acidosis correction and cardiovascular stability. Contrib Nephrol. 1994;108:105–13.
48. Santoro A, Panzetta G, Tessitore N, Atti M, Mancini E, Esteban J, London G, Ara JM, Miguel JL, Neumann KH, Opatrny K, Perez R, Perrone B, Wizemann V, Zucchelli P. A prospective randomised European multicentre study of medium-long run mortality and morbidity comparing acetate-free biofiltration and bicarbonate dialysis. J Nephrol. 1999;12(6):375–82.
49. Ghezzi PM, Frigato G, Fantini GF, Dutto A, Meinero S, Cento G, Marazzi F, D'Andria V, Grivet V. Theoretical model and first clinical results of the paired filtration-dialysis (PFD). Life Support Syst. 1983;1 Suppl 1:271–4.
50. Ghezzi PM. Hemodiafiltration with endogenous reinfusion (HFR): evolution of the method. G Ital Nefrol. 2005;22 Suppl 31:S105–10.
51. European best practice guidelines for haemodialysis (part 1). Section IV: dialysis fluid purity. Nephrol Dial Transplant. 2002;17(Suppl 7):45–61.
52. Quality of dialysis fluid for haemodialysis and related therapies. ISO 11663:2009–2014.
53. Shinzato T, Sezaki R, Usuda M, Maeda K, Ohbayashi S, Toyota T. Infusion-free hemodiafiltration: simultaneous hemofiltration and dialysis with no need for infusion fluid. Artif Organs. 1982;6(4):453–6.
54. Shinzato T, Kobayakawa H, Maeda K. Comparison of various treatment modes in terms of beta 2-microglobulin removal: hemodialysis, hemofiltration, and push/pull HDF. Artif Organs. 1989;13(1):66–70.

55. Miller JH, von Albertini B, Gardner PW, Shinaberger JH. Technical aspects of high-flux hemodiafiltration for adequate short (under 2 hours) treatment. Trans Am Soc Artif Intern Organs. 1984;30:377–81.
56. von Albertini B, Miller JH, Gardner PW, Shinaberger JH. Performance characteristics of the hemoflow F 60 in high-flux hemodiafiltration. Contrib Nephrol. 1985;46:169–73.
57. Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. Kidney Int. 2010;77(7):581–7.
58. Rabindranath KS, Strippoli GF, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: systematic review. Am J Kidney Dis. 2005;45(3):437–47.
59. Cappelli G, Perrone S, Ciuffreda A. Water quality for on-line haemodiafiltration. Nephrol Dial Transplant. 1998;13 Suppl 5:12–6.
60. Di Felice A, Cappelli G, Facchini F, Tetta C, Cornia F, Aimo G, Lusvarghi E. Ultrafiltration and endotoxin removal from dialysis fluids. Kidney Int Suppl. 1993;41:S201–4.
61. Vaslaki L, Karátson A, Vörös P, Major L, Pethö F, Ladányi E, Weber C, Mitteregger R, Falkenhagen D. Can sterile and pyrogen-free on-line substitution fluid be routinely delivered? A multicentric study on the microbiological safety of on-line haemodiafiltration. Nephrol Dial Transplant. 2000;15 Suppl 1:74–8.
62. Penne EL, Visser L, van den Dorpel MA, van der Weerd NC, Mazairac AH, van Jaarsveld BC, Koopman MG, Vos P, Feith GW, Kremer Hovinga TK, van Hamersvelt HW, Wauters IM, Bots ML, Nubé MJ, Ter Wee PM, Blankestijn PJ, Grooteman MP. Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. Kidney Int. 2009;76(6):665–72.
63. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, Levesque R, ter Wee PM, Nubé MJ, Blankestijn PJ, van den Dorpel MA, CONTRAST Investigators. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86(2):423–32.
64. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58(2):809–17.
65. Lee K, Jeong JH, Mun CH, Lee SR, Yoo KJ, Park YW, Won YS, Min BG. Convection-enhanced high-flux hemodialysis. Artif Organs. 2007;31(8):653–8.
66. Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN. Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. Kidney Int. 1985;28(3):535–40.
67. Leunissen KM, Hoorntje SJ, Fiers HA, Dekkers WT, Mulder AW. Acetate versus bicarbonate hemodialysis in critically ill patients. Nephron. 1986;42(2):146–51.
68. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlandini G. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. Kidney Int. 1996;50(4):1293–302.
69. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. Kidney Int. 1999;55(1):286–93.
70. Dr Devil. Hemodialysis vs. Hemodiafiltration…the future..or another fad? http://ihatedialysis.com/forum/index.php?PHPSESSID=fb10a0c1341ebd2ae0f07af65de46e94&topic=1502.msg18977#msg18977.
71. Blankestijn PJ. Is hemodiafiltration medically superior to hemodialysis? Semin Dial. 2014;27(3):248–9.
72. Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, et al. A new form of amyloid protein associated with chronic hemodialysis was identified as beta 2-microglobulin. Biochem Biophys Res Commun. 1985;129(3):701–6.
73. Gejyo F, Odani S, Yamada T, Honma N, Saito H, Suzuki Y, Nakagawa Y, Kobayashi H, Maruyama Y, Hirasawa Y, et al. Beta 2-microglobulin: a new form of amyloid protein associated with chronic hemodialysis. Kidney Int. 1986;30(3):385–90.

74. Bardin T, Zingraff J, Shirahama T, Noel LH, Droz D, Voisin MC, Drueke T, Dryll A, Skinner M, Cohen AS, et al. Hemodialysis-associated amyloidosis and beta-2 microglobulin. Clinical and immunohistochemical study. Am J Med. 1987;83(3):419–24.
75. Bardin T, Zingraff J, Kuntz D, Drüeke T. Dialysis-related amyloidosis. Nephrol Dial Transplant. 1986;1(3):151–4.
76. Zingraff J, Beyne P, Ureña P, Uzan M, Nguyen Khoa Man, Descamps-Latscha B, Drüeke T. Influence of haemodialysis membranes on beta 2-microglobulin kinetics: in vivo and in vitro studies. Nephrol Dial Transplant. 1988;3(3):284–90.
77. van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J. Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int. 1991;39(5):1012–9.
78. Schwalbe S, Holzhauer M, Schaeffer J, Galanski M, Koch KM, Floege J. Beta 2-microglobulin associated amyloidosis: a vanishing complication of long-term hemodialysis? Kidney Int. 1997;52(4):1077–83.
79. Canaud B, Assounga A, Kerr P, Aznar R, Mion C. Failure of a daily haemofiltration programme using a highly permeable membrane to return beta 2-microglobulin concentrations to normal in haemodialysis patients. Nephrol Dial Transplant. 1992;7(9):924–30.
80. Kerr PB, Argilés A, Flavier JL, Canaud B, Mion CM. Comparison of hemodialysis and hemodiafiltration: a long-term longitudinal study. Kidney Int. 1992;41(4):1035–40.
81. Kerr PG, Argiles A, Canaud B, Flavier JL, Mion C. The effects of reprocessing high-flux polysulfone dialyzers with peroxyacetic acid on beta 2-microglobulin removal in hemodiafiltration. Am J Kidney Dis. 1992;19(5):433–8.
82. Lornoy W, Becaus I, Billiouw JM, Sierens L, van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18(2):105–8.
83. Altieri P, Sorba G, Bolasco P, Asproni E, Ledebo I, Cossu M, Ferrara R, Ganadu M, Cadinu F, Serra G, Cabiddu G, Sau G, Casu D, Passaghe M, Bolasco F, Pistis R, Ghisu T, Second Sardinian Multicentre Study. Predilution haemofiltration: the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical Kt/V and session times in a long-term cross-over study. Nephrol Dial Transplant. 2001;16(6):1207–13.
84. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant. 2000;15 Suppl 1:43–8.
85. Barth RH. Dialysis by the numbers: the false promise of Kt/V. Semin Nephrol. 1989;2: 207–12.
86. Greene T, Beck GJ, Gassman JJ, Gotch FA, Kusek JW, Levey AS, Levin NW, Schulman G, Eknoyan G. Design and statistical issues of the hemodialysis (HEMO) study. Control Clin Trials. 2000;21(5):502–25.
87. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R, Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25): 2010–9.
88. Nakai S, Iseki K, Tabei K, Kubo K, Masakane I, Fushimi K, Kikuchi K, Shinzato T, Sanaka T, Akiba T. Outcomes of hemodiafiltration based on Japanese dialysis patient registry. Am J Kidney Dis. 2001;38(4 Suppl 1):S212–6.
89. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R, RISCAVID Study Group. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. Nephrol Dial Transplant. 2008;23(7):2337–43.
90. Jirka T, Cesare S, Di Benedetto A, Perera Chang M, Ponce P, Richards N, Tetta C, Vaslaky L. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int. 2006;70(8):1524.
91. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4(12):1944–53.

92. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69(11):2087–93.
93. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ, CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23(6):1087–96.
94. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M, Turkish Online Haemodiafiltration Study. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
95. Penne EL, van der Weerd NC, Bots ML, van den Dorpel MA, Grooteman MP, Lévesque R, Nubé MJ, Ter Wee PM, Blankestijn PJ, CONTRAST investigators. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. Nephrol Dial Transplant. 2009;24(11):3493–9.
96. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
97. Tattersall JE, Ward RA, EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542–50.
98. Canaud B, Bowry SK. Emerging clinical evidence on online hemodiafiltration: does volume of ultrafiltration matter ? Blood Purif. 2013;35(1–3):55–62.
99. Bowry SK, Canaud B. Achieving high convective volumes in on-line hemodiafiltration. Blood Purif. 2013;35 Suppl 1:23–8.
100. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nubé MJ, van der Tweel I, Ter Wee PM, the CONTRAST study group. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients – the Dutch CONvective TRAnsport Study (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Control Trials Cardiovasc Med. 2005;6(1):8.
101. Sichart JM, Moeller S. Utilization of hemodiafiltration as treatment modality in renal replacement therapy for end-stage renal disease patients: a global perspective. Contrib Nephrol. 2011;175:163–9.
102. Golper TA. Technological advances. Semin Dial. 1994;7:323–4.
103. Blankestijn PJ. Has the time now come to more widely accept hemodiafiltration in the United States? J Am Soc Nephrol. 2013;24(3):332–4.
104. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, Delcourt C, Papoz L, Descomps B, Canaud B. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17(3):422–7.